31; page 24, line 11 to page 25, line 2 of the substitute specification. Support for claim 47 is found on page 24, lines 30-31 of the substitute specification. Support for claim 48 is found on page 27, lines 26-27 of the substitute specification. Support for claim 49 is found on page 27, lines 28-29 of the substitute specification. Applicants respectfully submit that no new matter is introduced by the present Amendment.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 12-44 under 35 U.S.C. §112, first paragraph. In addition, in the interview of April 3, 2002, the Examiner suggested that the recitation of gene therapy in the claims was objectionable. Applicants traverse the rejection to the extent it is applied to the claims as amended.

Applicants respectfully disagree with the Examiner's rejection for the reasons set forth in our response to Office Action filed July 13, 2001. Contrary to the Examiner's contention, Applicants reiterate that there is no reason to believe that their methods for designing and using a suppression effector for the suppression of a mutant allele of a gene and a replacement allele, would not work *in vivo* for suppressing a gene and replacing it with a non-disease causing gene, given the state of the art of ribozymes and gene therapy.

Nevertheless, without acquiescing to the merits of the rejection but in order to promote prosecution, Applicants have removed the objectionable language from the claims. Applicants submit that the rejections under 35 U.S.C. §112, first paragraph do not apply to the amended and new claims. The amended and new claims do not recite an *in vivo* use.

While examples are not required, Applicants have provided several detailed examples of *in vitro* use that enable the claims as amended. For example, the instant specification provides adequate guidance pertaining to (1) how to choose an appropriate target site for a ribozyme by analyzing RNA folding, (2) the design and construction of several ribozymes that reliably and reproducibly hybridize to and cleave RNA encoded by mammalian rhodopsin, peripherin and collagen genes *in vitro*, and (3) the inability of the ribozyme to cleave replacement nucleic acids that are modified at degenerate /

wobble base positions and are thereby protected from suppression. For example, pages 19-20 of the Applicants' specification teach how a ribozyme target site can be chosen based on the presence of a ribozyme target sequence and the robustness of the two dimensional loop structure of the RNA in which the target sequence lies, as is determined by art known methods such as RNAPlotFold analysis. Pages 18-24 teach standard methods for cloning cDNA templates and ribozymes into a suitable expression vectors. Pages 25-34 teach detailed descriptions of the cleavage of exemplary mutations targeted by the exemplary ribozymes. The figures and results of Applicants' actual experiments on pages 37-49 teach that the exemplary ribozymes reproducibly cleave RNA comprising a ribozyme target site but do not cleave modified normal or non-disease-causing RNA, because the RNA does not contain the ribozyme target site. Applicants thus provide a method for designing suppression effectors, such as ribozymes, that destroy a target RNA and replace it with a replacement nucleic acid that has been altered in one or more degenerate / wobble bases. By exploiting the redundancy of the genetic code or the "wobble hypothesis", recognition or cleavage by the suppression effector is blocked but a normal or non-disease-causing protein is encoded by the replacement nucleic acid.

Applicants therefore respectfully submit that the specification is sufficient to enable one having an ordinary skill in the art, given the high level of skill in the art at the filing date of the instant application, to make and use the invention as now claimed without undue experimentation. Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

CONCLUSION

Applicants request that the Examiner consider the claims as amended and prompt and favorable action on the instant application.

Request for a Telephonic Interview

Applicants hereby request a telephonic interview with the Examiner in order to expedite the favorable prosecution of the case. The Examiner is invited to phone the

undersigned to arrange for a convenient time to discuss any outstanding issue, and to work with the undersigned toward placing the application in condition for allowance.

Respectfully submitted,

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MARKED-UP VERSION OF AMENDED CLAIMS

12. (Amended) A method for designing a [therapeutic useful for treating a genetic disease] suppression effector and replacement nucleic acid, said method comprising:

a) determining at least a portion of a nucleotide sequence of a mutant allele;

b) designing a suppression effector that binds to [the] said portion[of the nucleotide sequence], thereby to inhibit the expression of the mutant allele; and

c) designing a replacement nucleic acid which varies from the mutant allele by having one or more degenerate / wobble sites that are altered so that the replacement nucleic acid is not inhibited by the suppression effector,

wherein the replacement nucleic acid encodes a wild-type or non-disease causing protein.

13. (Amended) A method for designing a [therapeutic useful for treating a genetic disease] suppression effector and replacement nucleic acid, the method comprising:

a) determining at least a portion of a nucleotide sequence of a mutant allele;

b) identifying the presence of a ribozyme cleavage site on the mutant allele;

c) designing a ribozyme that cleaves an RNA encoded by the mutant allele; and

d) designing a replacement nucleic acid which is not suppressed or is only partially suppressed,

wherein the replacement nucleic acid differs from the mutant allele in at least one degenerate / wobble position of at least one codon and wherein the replacement nucleic acid encodes a wild-type or non-disease causing protein.

23. Canceled.

24. Canceled.

27. (Amended) The method of claim 21 or 26, wherein the expression vector is a viral expression vector.

28. Canceled.

29. Canceled.

30. (Amended) The [therapeutic of claim 28] kit of claim 44, wherein the suppression effector is a nucleic acid or a peptide nucleic acid (PNA).

31. (Amended) The [therapeutic of claim 28] kit of claim 44, wherein the suppression effector is a peptide or an antibody.

32. (Amended) The [therapeutic of claim 28] kit of claim 44, wherein the suppression effector is a nucleic acid that forms a triple helix with the mutant allele.

33. (Amended) The [therapeutic of claim 28] kit of claim 44, wherein the suppression effector is an antisense nucleic acid.

34. (Amended) The [therapeutic of claim 28] kit of claim 44, wherein the suppression effector is a single-stranded RNA.

35. (Amended) The [therapeutic of claim 28] kit of claim 44, wherein the suppression effector is a ribozyme which cleaves an RNA encoded by the mutant allele.

36. (Amended) The [therapeutic] kit of claim 35, wherein the ribozyme cleaves an RNA encoded by the mutant allele at an NUX ribozyme cleavage site.

37. (Amended) The [therapeutic of claim 28 or 29] kit of claim 44 or 45, wherein the suppression effector is operatively linked to an expression vector.

38. (Amended) The [therapeutic of claim 28 or 29] kit of claim 44 or 45, wherein the suppression effector binds to the mutant allele in one or more sites selected from the group consisting of a coding region, a 5' untranslated region, a 3' untranslated region and an intronic region.

39. Canceled.

40. Canceled.

41. (Amended) The [therapeutic of claim 28 or 29] kit of claim 44 or 45, wherein the replacement nucleic acid encodes a protein selected from the group consisting of mammalian rhodopsin, collagen 1A1, collagen 1A2 and peripherin.

42. (Amended) The [therapeutic of claim 28 or 29] kit of claim 44 or 45, wherein the replacement nucleic acid is operatively linked to an expression vector.

43. (Amended) The [therapeutic] kit of claim 42, wherein the expression vector is a viral expression vector.

44. (Amended) A kit [comprising a therapeutic for the treatment of a genetic disease linked to a mutation in a gene, the kit] comprising:

a suppression effector that suppresses the expression of a mutant allele; and

a replacement nucleic acid which differs from the mutant allele in at least one degenerate / wobble position of at least one codon and wherein the replacement nucleic acid encodes a wild-type or non-disease causing protein.

45. (New) A kit comprising:

at least one ribozyme that cleaves an RNA encoded by the mutant allele; and

a replacement nucleic acid which is not suppressed or is only partially suppressed, wherein the replacement nucleic acid differs from the mutant allele in at least one degenerate / wobble position of at least one codon and wherein the replacement nucleic acid encodes a wild-type or non-disease causing protein.

46. (New) A ribozyme comprising nucleotides 101 - 137 of SEQ ID NO:4.

47. (New) A ribozyme comprising nucleotides 116 - 153 of SEQ ID NO:14.

48. (New) A ribozyme comprising nucleotides 112 - 148 of SEQ ID NO:15.

49. (New) A ribozyme comprising nucleotides 107 - 141 of SEQ ID NO:18.